111 - 1090

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of: Jeffrey Wenig

Patent No.: 4,724,231

Serial No.: 06/848,690

For: NASAL COMPOSITIONS CONTAINING VITAMIN B_{12}

Docket: 719-69

Issued: February 9, 1988

Filed: April 8, 1986

Date: January 3, 1997

EXPRESS MAIL CERTIFICATE

Date 1-3-97 Label No. EM290462959US

I hereby certify that on the date indicated above, I deposited this paper or fee with the U.S. Postal Service & that it was addressed for delivery to the Assistant Commissioner for Patents, Washington, D.C. 20231 by "EXPRESS MAIL Post Office to Addressee" service.

Kim Beaulieu Kim Beaulieu

Name (Print) Signature

Box Patent Ext.
Assistant Commissioner for Patents
Washington, D.C. 20231

LETTER OF TRANSMITTAL OF APPLICATTON FOR EXTENSION OF PATENT TERM

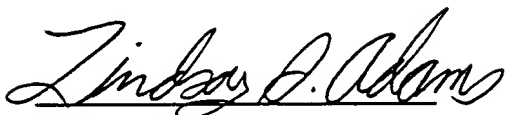
Sir:

Transmitted herewith is an application for extension of the patent term under 35 U.S.C. §156 for U.S. Patent No.: 4,724,231. The application includes Exhibits A-C, a Declaration pursuant to 37 C.F.R. §1.740(b), a Power of Attorney executed by the Applicant, and a duplicate of the application papers, certified as such.

The filing fee of $1090.00 in accordance with 37 C.F.R. § 1.20(j) is also enclosed herewith. The Commissioner is hereby authorized to charge any additional fees, or credit

any overpayment, to Deposit Account No.: 08-2461. Two additional copies of this sheet are enclosed.

Respectfully submitted,



Lindsay S. Adams
Attorney for Applicant
Registration No.: 36,425

Hoffmann & Baron
350 Jericho Turnpike
Jericho, New York 11753
(516) 822-3550

1CC

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of: Jeffrey Wenig

Patent No.: 4,724,231

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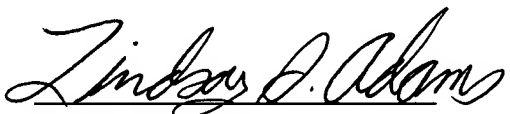
Respectfully submitted,



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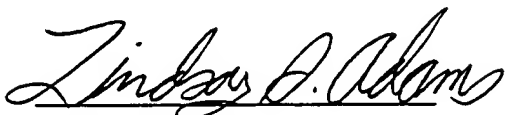

Lindsay S. Adams
Attorney for Applicant
Registration No.: 36,425

Hoffmann & Baron
350 Jericho Turnpike
Jericho, New York 11753
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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of: Jeffrey Wenig

Patent No.: 4,724,231

Serial No.: 06/848,690

For: NASAL COMPOSITIONS CONTAINING VITAMIN B_{12}

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Box Patent Ext.
Assistant Commissioner for Patents
Washington, D.C. 20231

DECLARATION PURSUANT TO 37 C.F.R. §1.740(b) FOR APPLICATION FOR PATENT EXTENSION UNDER 35 U.S.C. §156

Sir:

The undersigned, an Attorney registered to practice before the U.S. Patent and Trademark Office and having the general authority from the owners of U.S. Patent No. 4,724,231 to act on behalf of the owners of said patent (i.e., the Applicant), as indicated in the Power of Attorney being submitted herewith, hereby states:

1. I have reviewed and understand the contents of the application for patent extension of U.S. Patent No. 4,724,231 being submitted herewith pursuant to 35 U.S.C. §156;

2. I believe U.S. Patent No. 4,724,231 is subject to an extension pursuant to 37 C.F.R. §1.710 and believe that the term of extension claimed in the

application filed contemporaneously herewith is justified under 35 U.S.C. §156 and under the applicable regulations; and

3. I believe that U.S. Patent No. 4,724,231 for which an extension is being sought meets all the conditions for an extension of the term of said patent, as set forth in 37 C.F.R. §1.720.

I further state that the above statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that any willful false statements may jeopardize the validity of this patent.

Date: 1/3/97

Respectfully submitted,

Lindsay S. Adams

Lindsay S. Adams
Registration No.: 36,425
Attorney for Applicant

HOFFMANN & BARON
350 Jericho Turnpike
Jericho, New York 11753
(516) 822-3550
LSA/kb

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of: Jeffrey Wenig

Patent No.: 4,724,231

Serial No.: 06/848,690

For: NASAL COMPOSITIONS CONTAINING VITAMIN B_{12}

Box Patent Ext.
Assistant Commissioner for Patents
Washington, D.C. 20231

Docket: 719-69

Issued: February 9, 1988

Filed: April 8, 1986

POWER OF ATTORNEY BY ASSIGNEE OF ENTIRE INTEREST

Sir:

Nastech Pharmaceutical Company Inc., of 45 Davids Drive, Hauppauge, New York 11788, as assignee of record of U.S. Patent No.: 4,724,231, hereby appoints the following attorneys:

Charles R. Hoffmann, Reg. No. 24,102; Ronald J. Baron, Reg. No. 29,281; Gerald T. Bodner, Reg. No. 30,449; Alan M. Sack, Reg. No. 31,874; A. Thomas Kammer, Reg. No. 28,226; Arlene D. Morris, Reg. No. 32,657; R. Glenn Schroeder, Reg. No. 34,720; Glenn T. Henneberger, Reg. No. 36,074; Livia Boyadjian, Reg. No. 34,781; Sean W. O'Dea, Reg. No. 37,690; Lindsay S. Adams, Reg. No. 36,425; Paul J. Otterstedt, Reg. No. 37,411; Irving N. Feit, Reg. No. 28,601; William E. Lewis, Reg. No. 39,274; and Paul D. Ackerman, Reg. No. 39,891, each of them of HOFFMANN & BARON, 350 Jericho Turnpike, Jericho, New York 11753; and Daniel A. Scola, Jr., Reg. No. 29,855; Salvatore J. Abbruzzese, Reg. No. 30,152; Kirk M. Miles, Reg. No. 37,891; Kevin C. Hooper, Reg. No. P-40,402; and Robert F. Chisolm, Reg. No. 39,939, each of them of HOFFMANN & BARON, 1055 Parsippany Boulevard, Parsippany, New Jersey 07054,

to apply for an extension of the term of said patent, to make alterations and amendments therein, and transact all business in the U.S. Patent and Trademark Office connected therewith, and request that all further correspondence be conducted with Hoffmann & Baron as indicated below.

SEND CORRESPONDENCE TO:

Gerald T. Bodner, Esq.
Hoffmann & Baron
350 Jericho Turnpike
Jericho, New York 11753

DIRECT TELEPHONE CALLS TO:

Lindsay S. Adams, Esq.

Nastech PharmaceuticalCompany, Inc.
(type or print identity of assignee of entire interest)

45 Davids Drive
Address

Hauppauge, New York 11788

[X] Recorded in PTO on April 8, 1986
Reel 4567
Frame 732

[ ] Recorded herewith

ASSIGNEE CERTIFICATION UNDER 37 CFR 3.73(b)

I, the undersigned, have reviewed all the documents in the chain of title of the patent matter identified above and, to the best of my knowledge and belief, title is in the assignee identified above.

I, hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements, and the like so made, are punishable by fine or imprisonment, or both, under Section 1001, Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the patent.

(Signature)

Date 1/23/97

Vincent D. Romeo R. Ph., Ph.D.
(type or print name of person authorized to sign on behalf of assignee)

President and CEO
Title

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of: Jeffrey Wenig

Docket: 719-69

Patent No.: 4,724,231

Issued: February 9, 1988

Serial No.: 06/848,690

Filed: April 8, 1986

For: NASAL COMPOSITIONS CONTAINING VITAMIN B_{12}

Date: January 3, 1997

Box Patent Ext.
Assistant Commissioner for Patents
Washington, D.C. 20231

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

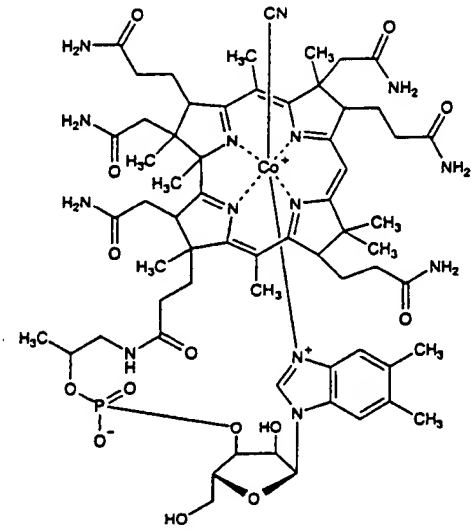
Sir:

Applicant, Nastech Pharmaceutical Company Inc., of 45 Davids Drive, Hauppauge, New York 11788, represents that it is the assignee of the entire interest in and to Letters Patent of the United States No.: 4,724,231, issued to Jeffrey Wenig, by virtue of an assignment to Nastech Pharmaceutical Company Inc., recorded on April 8, 1986 at Reel 4567, starting at Frame 0732.

Applicant hereby submits this application for extension of patent term under 35 U.S.C. §156, by providing the following information as required by 37 C.F.R. §1.740.

(1) The approved product is NASCOBAL™ (Cyanocobalamin, USP), Gel for Intranasal Administration, in which the sole active ingredient is Cyanocobalamin (generic name). The chemical name for the active ingredient is 5,6-dimethyl-benzimidazolyl

cyanocobamide, which has a molecular formula of $C_{63}H_{88}CoN_{14}O_{14}P$, a molecular weight of 1355.38 and the following structure:



(2) The approved product was subject to regulatory review under the Federal Food, Drug, and Cosmetic Act (21 U.S.C. §355), Section 505.

(3) NASCOBAL™ received its first and only permission for commercial marketing or use under Section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. §355) on November 5, 1996.

(4) As previously described in paragraph (1), the approved product, NASCOBAL™, which is a human drug, contains Cyanocobalamin as its sole active ingredient. This active ingredient has been previously approved for commercial marketing or use under Section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. §355) for use in compositions other than Applicant's Gel for Intranasal Administration.

(5) This application for extension of patent term under 35 U.S.C. §156 is being submitted within the sixty (60) day period permitted for submission, the last day for said submission being January 4, 1997.

(6) The complete identification of the patent for which an extension is being sought is as follows:

Inventor: Jeffrey Wenig

Patent No.: 4,724,231

Issued: February 9, 1988

Expiration: February 9, 2005

(7) A copy of the patent for which an extension is being sought is attached herewith as "Exhibit A."

(8) No Disclaimer, Certificate of Correction or Reexamination Certificate has been filed or issued with respect to U.S. Patent No.: 4,724,231. Two (2) receipts of maintenance fee payments have been issued for U.S. Patent No.: 4,724,231, and are attached herewith as "Exhibit B."

(9) U.S. Patent No.: 4,724,231 claims various compositions that reads on the approved product, NASCOBAL™ (Cyanocobalamin, USP), Gel for Intranasal Administration, and also claims methods of using said compositions for the treatment of patients suffering from Vitamin B_{12} deficiency.

(a) The approved product is an isotonic aqueous gel solution having a therapeutically effective amount of Vitamin B_{12} (i.e., 500 mcg of Cyanocobalamin per dosage unit), a citrate/citric acid buffer, 2.23 wt. % of a glycerin humectant, a methylcellulose thickening agent, 0.02 wt.% of a benzalkonium chloride preservative, a pH between 4.5 to 5.5, and a viscosity ranging from 2,500 to 10,000 cps. The approved product has been granted permission for use in the treatment of patients suffering from a deficiency of Vitamin B_{12} and its associated symptoms.

(b) The following claims cover the approved product or the method of using the approved product. Claims 1-3, 6-7, 9-11, 14-15, and 25-26 of U.S. Patent No.: 4,724,231 all read on (i.e., cover) the approved product. Claims 17-19, 22-23, and 27 of U.S. Patent No.: 4,724,231 all read on (i.e., cover) the use of the approved product for the treatment humans suffering from a Vitamin B_{12} deficiency.

(10) The relevant dates and information pursuant to 35 U.S.C. §156 to enable the Secretary of Health and Human Services to determine the length of the applicable regulatory review period are listed below.

(a) U.S. Patent No.: 4,724,231 was issued on February 9, 1988.

(b) An application for Investigational New Drug exemption ("IND") for NASCOBAL™ was submitted to the FDA on January 21, 1985, and assigned IND No.: 25,696.

(c) IND No.: 25,696 was deemed to have an effective filing date of February 21, 1985.

(d) A New Drug Application ("NDA") for NASCOBAL™ was deemed submitted to the FDA on September 11, 1987, and assigned NDA No.: 19-722.

(e) NDA No.: 19-722 for NASCOBAL™ was approved on November 5, 1996.

(11) A brief description of the activities undertaken by the Applicant during the applicable regulatory review period with respect to NASCOBAL™ and the significant dates applicable to such activities is attached herewith as "Exhibit C."

(a) Applicant submits that the entire period from January 21, 1985, through November 5, 1996, the data generated on this product was for submission to the FDA in support of the NDA. Moreover, Applicant submits that it acted with due diligence during the entire regulatory review period.

(12) Applicant is of the opinion that U.S. Patent No.: 4,724,231 is eligible for extension under 35 U.S.C. §156 because it satisfies the requirements for such extension as follows.

(a) Pursuant to 35 U.S.C. §156(a), U.S. Patent 4,724,231 claims a product and a method of using a product.

(b) Pursuant to 35 U.S.C. §156(a)(1), the term of U.S. Patent No.: 4,724,231 has not expired before submission of this application for extension.

(c) Pursuant to 35 U.S.C. §156(a)(2), the term of U.S. Patent No.: 4,724,231 has never been extended.

(d) Pursuant to 35 U.S.C. §156(a)(3), the application for extension is submitted by the agent of the owner of record of U.S. Patent No.: 4,724,231, Nastech Pharmaceutical Company Inc., in accordance with the requirements of 35 U.S.C. §156(d) and the guidelines of the U.S. Patent and Trademark Office.

(e) Pursuant to 35 U.S.C. §156(a)(4), the approved product, NASCOBAL™, has been subject to regulatory review period before its commercial marketing or use.

(f) Pursuant to 35 U.S.C. §156(a)(5)(A), the permission for the commercial marketing or use of the approved product, NASCOBAL™, after the regulatory review period is the first permitted commercial marketing or use of the product under the provision of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355), under which such regulatory review period occurred.

(g) Pursuant to 35 U.S.C. §156(c)(4), no other patent has been extended for the same regulatory review period for the approved product, NASCOBAL™.

(h) The length of extension of the patent term of U.S. Patent No.: 4,724,231 claimed by Applicant is five (5) years, the maximum possible under 35 U.S.C. §156(g)(6)(A), since the patent involved was issued after the date of enactment of 35 U.S.C. §156, and the regulatory review period that occurred after the date of patent issuance exceeded five (5) years. The manner in which the term of extension that Applicant is entitled to was calculated as shown below.

(1) Pursuant to 35 U.S.C. §156(g)(l)(B), Applicant's total regulatory review period is the combination of the "testing phase" under 35 U.S.C. §156(g)(l)(B)(i) and the "approval phase" under 35 U.S.C. §156(g)(1)(B)(ii). This time period is approximately 11 years and 7.5 months. Applicant's testing phase was from January 21, 1985 until September 11, 1987, which is approximately 2 years and 7.2 months. Applicant's approval phase was from September 11, 1987, until November 5, 1996, which is approximately 9 years and 0.3 months.

(2) Pursuant to 35 U.S.C. §156(c), Applicants are only entitled to a term extension for the regulatory review period that occurred after the issuance of U.S. Patent No.: 4,724,231, which was from February 10, 1988 until November 5, 1996, approximately 7 years and 9 months. This term is subject to the limitations described below.

(3) The regulatory review period after patent issuance, 7 years and 9 months, is subject to the limitations of 35 U.S.C. §156(c)(3) and 35 U.S.C. §156(g)(6)(A). Therefore, the term of extension pursuant to 35 U.S.C. 156(c), may not exceed fourteen (14) years minus the remaining term of the patent, and may not exceed five (5) years.

(4) The remaining term of the U.S. Patent No.: 4,724,231 is approximately eight (8) years and two (2) months. Thus, pursuant 35 U.S.C. §156(c)(3), the term of patent extension is equal to 14 years minus 8 years and 2 months. This amount of time is approximately 5 years and 10 months.

(5) Because the term of patent extension cannot exceed five (5) years, pursuant to 35 U.S.C. §156(g)(6)(A), Applicant is entitled to a maximum term of patent extension of five (5) years.

(13) Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to any determination to be made relative to this application for extension.

(14) A check for the prescribed fee for receiving and acting upon this application for extension is enclosed herewith. If any additional fee is due, please charge our Deposit Account No. 08-2461 for such sum.

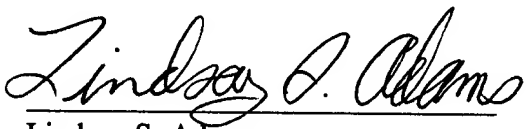
(15) The requisite Declaration, set forth in 37 C.F.R.§ 1.740(b) is also attached herewith.

(16) Inquiries and/or other correspondence relating to this application for patent term extension are to be directed to:

Gerald T. Bodner, Esq.
Hoffmann & Baron
350 Jericho Turnpike
Jericho, New York 11753

(17) A certified duplicate copy of the application papers is also being submitted herewith.

Respectfully submitted,



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Registration No.: 36,425

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(516) 822-3550

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D. C. 20231

HENRY T. BURKE
WYATT, GERBER, SHOUP AND BADIE
645 MADISON AVE., 5TH FLOOR
NEW YORK, NEW YORK 10022

DATE MAILED
09/10/91

165130

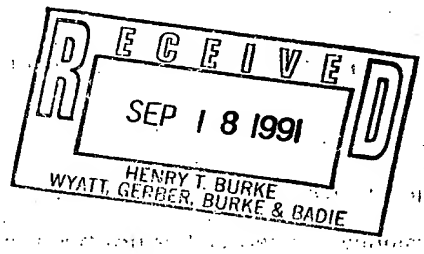
MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,724,231	273	415	----	06/848,690	02/09/88	04/08/86	04	YES	PAID



If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

ITM NBR	ATTY DKT NUMBER
1	17864A

**DIRECT THE RESPONSE TOGETHER WITH ANY QUESTIONS ABOUT THIS NOTICE TO:
COMMISSIONER OF PATENTS AND TRADEMARKS, BOX M. FEE, WASHINGTON, DC 20231**

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D. C. 20231

17864

75M7/0922

HENRY T. BURKE
WYATT, GERBER, SHOUP AND BADIE
645 MADISON AVE., 5TH FLOOR
NEW YORK, NEW YORK 10022

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ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,724,231	284	965	----	06/848,690	02/09/88	04/08/86	08	YES	PAID

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

Raotech

ITM NBR	ATTY DKT NUMBER
1	719-16 CIP 17864A

DIRECT THE RESPONSE TOGETHER WITH ANY QUESTIONS ABOUT THIS NOTICE TO:
COMMISSIONER OF PATENTS AND TRADEMARKS, BOX M. FEE, WASHINGTON, DC 20231

United States Patent [19]

Wenig

[11] **Patent Number: 4,724,231**

[45] **Date of Patent: Feb. 9, 1988**

[54] **NASEL COMPOSITIONS CONTAINING VITAMIN B_{12}**

[75] Inventor: **Jeffrey Wenig, Dix Hills, N.Y.**

[73] Assignee: **Nastech Pharmaceutical, Inc., Hauppauge, N.Y.**

[21] Appl. No.: **848,690**

[22] Filed: **Apr. 8, 1986**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 723,844, Apr. 16, 1985, abandoned.

[51] **Int. Cl.**[4] **A61K 31/70**
[52] **U.S. Cl.** **514/52**
[58] **Field of Search** 514/52; 424/45

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,174,295	11/1979	Bargigia et al.	424/45
4,525,341	6/1985	Deihl	514/52

OTHER PUBLICATIONS

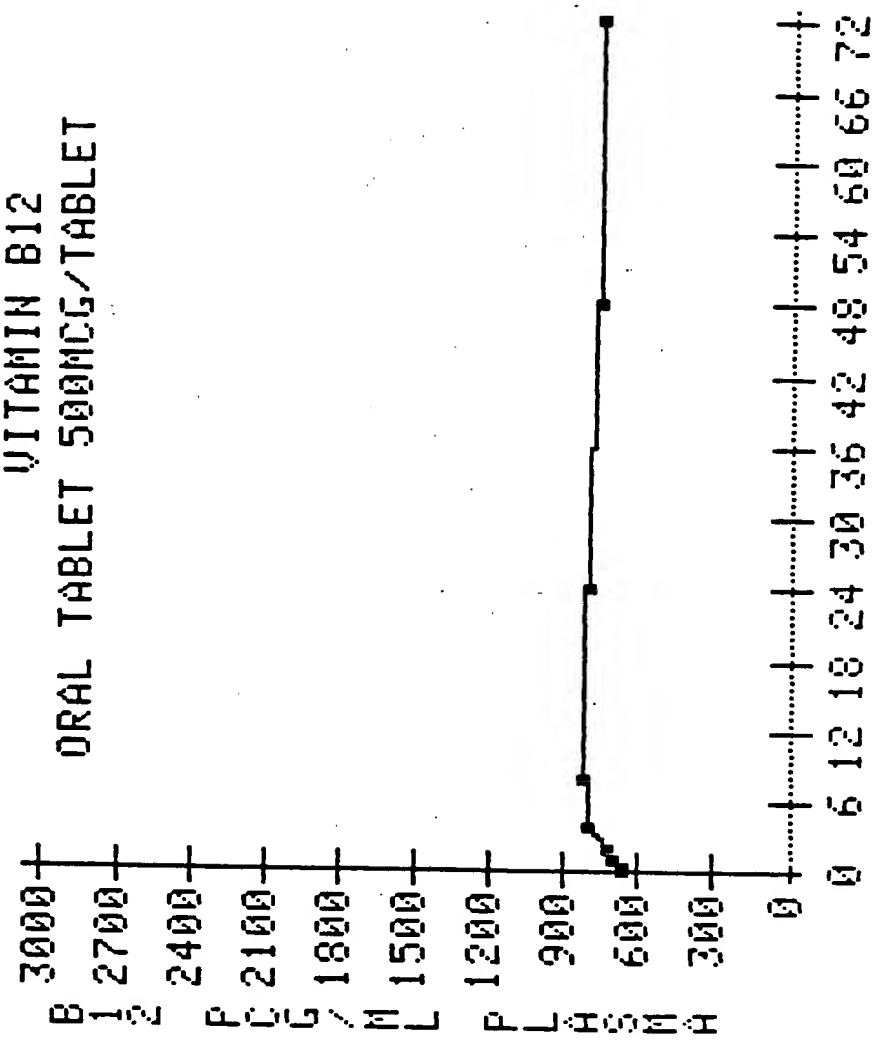
Chem. Abst. 66: 64246e (1967)–Shinton et al.
Chem. Abst. 77: 105,623y (1972)–Forest Laboratories.

Primary Examiner—Douglas W. Robinson
Attorney, Agent, or Firm—Wyatt, Gerber, Shoup, Scobey and Badie

[57] **ABSTRACT**

This invention is directed to compositions for nasal administration of a vitamin B_{12} to a human suffering a vitamin B_{12} deficiency. It is also directed to such compositions in dosage unit form and with methods of administering such compositions.

27 Claims, 4 Drawing Figures


VITAMIN B12
ORAL TABLET 500MCG/TABLET
B12 PG/ML
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2700
2400
2100
1800
1500
1200
900
600
300
0
0 6 12 18 24 30 36 42 48 54 60 66 72
HOURS POST DOSE

FIG.1

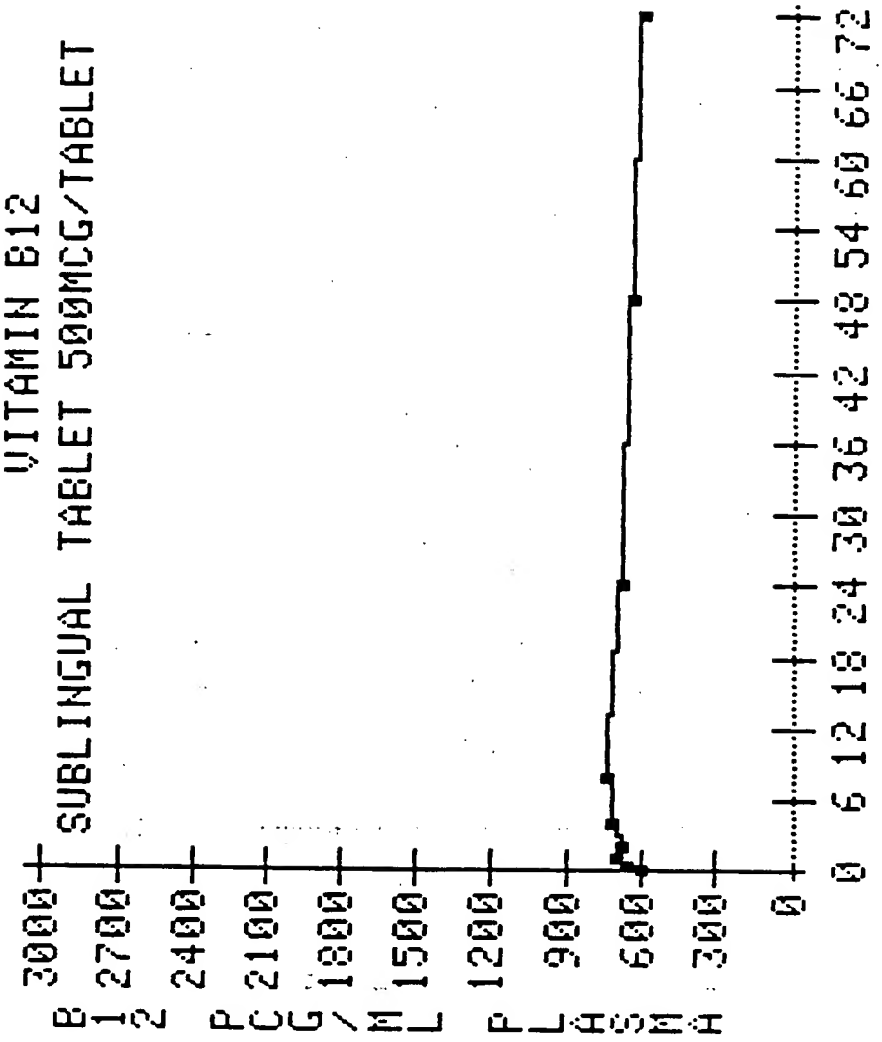
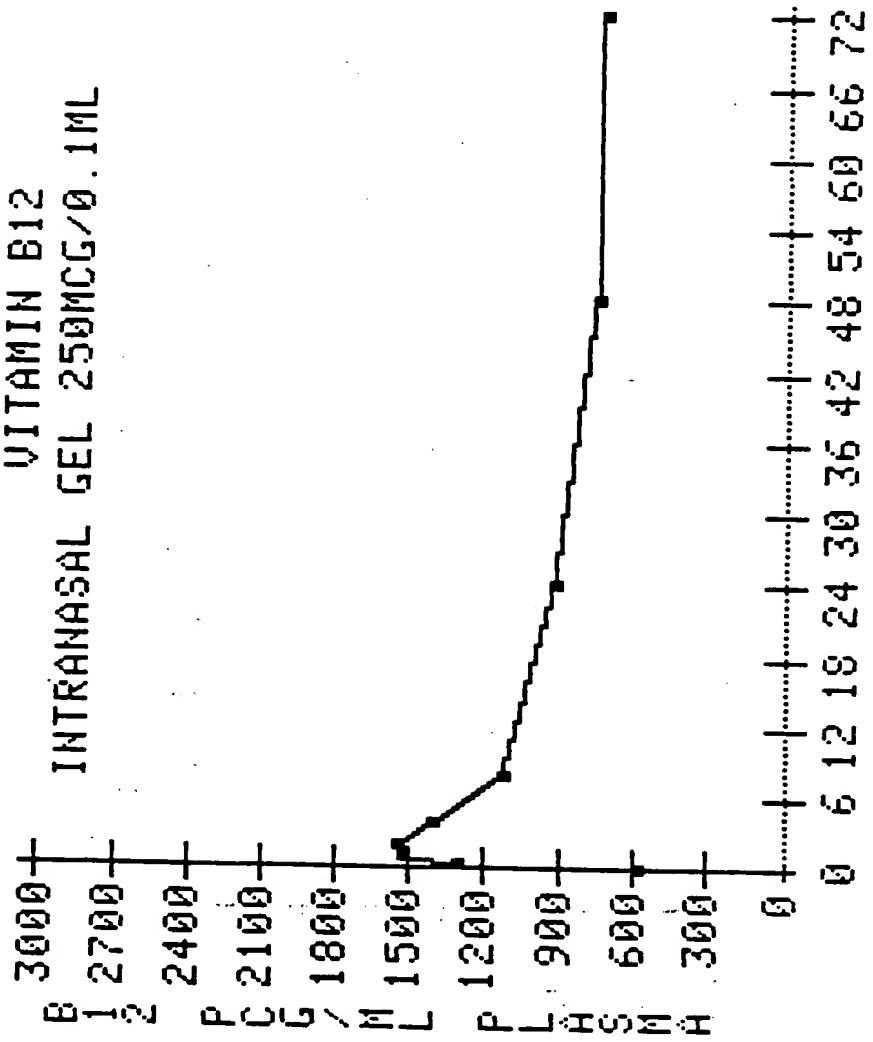

VITAMIN B12
SUBLINGUAL TABLET 500MCG/TABLET
B12 PCG/ML PLASMA
3000
2700
2400
2100
1800
1500
1200
900
600
300
0
0 6 12 18 24 30 36 42 48 54 60 66 72
HOURS POST DOSE

FIG.2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INTRANASAL GEL 250MCG/0.1ML
B12 PG/ML
3000
2700
2400
2100
1800
1500
1200
900
600
300
0
0 6 12 18 24 30 36 42 48 54 60 66 72
HOURS POST DOSE

FIG.3

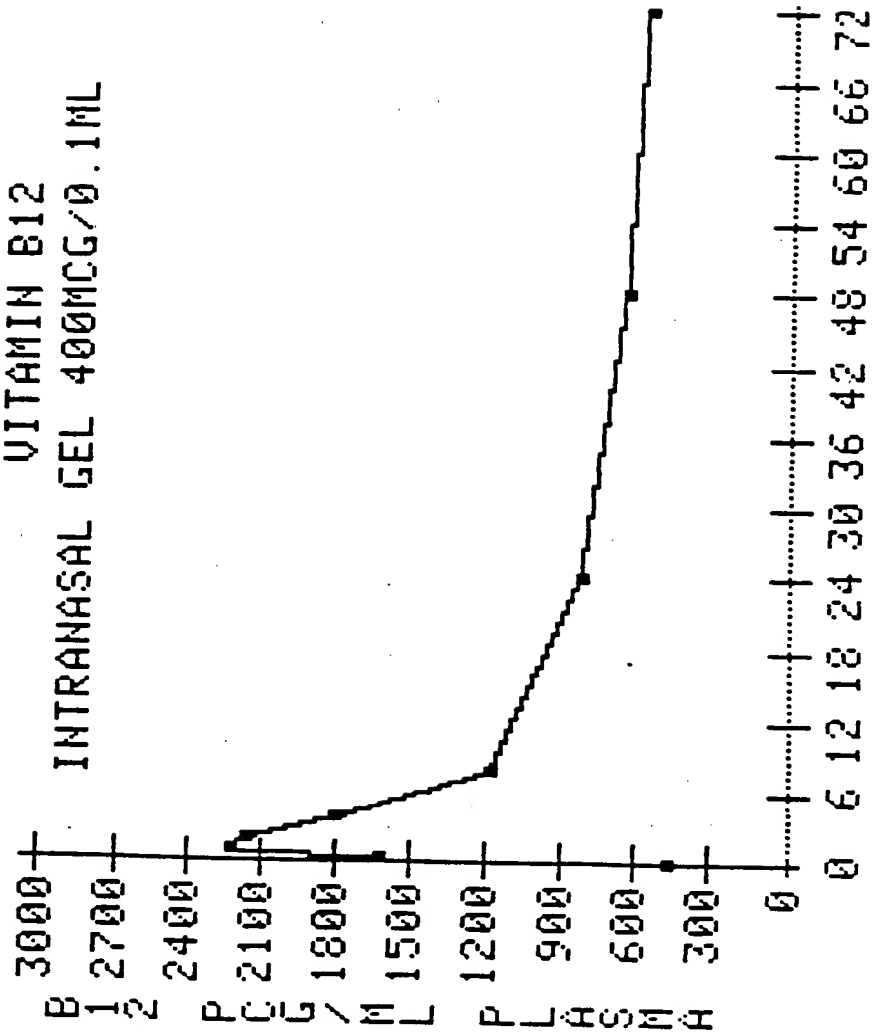
VITAMIN B12
INTRANASAL GEL 400MCG/0.1ML
B12 PG/ML PLASMA
3000
2700
2400
2100
1800
1500
1200
900
600
300
0
0 6 12 18 24 30 36 42 48 54 60 66 72
HOURS POST DOSE

FIG. 4

NASEL COMPOSITIONS CONTAINING VITAMIN B_{12}

BACKGROUND OF THE INVENTION

Cyanocobalamin is a vitamin B_{12}, and is one of the B_{12} class of vitamins which icnludes vitamin B_{12a} (hydroxocobalamin), vitamin B_{12b} (aquacobalamin), vitamin B_{12c} (nitrilocobalamin), coenzyme B_{12} (5'Odeoxyadenosine cobalamine) and methyl B_{12} (methyl cobalamine). Cyanocobalamin is the principal member of the class, and the most widely employed in medicine. This invention will be described as it relates to cyanocobalamin, but those skilled in the art will recognize that the invention is aplicable to the class.

Vitamin B_{12} is an essential compound for normal growth, hematopoiesis, production of all epithelial cells and maintenance of myelin throughout the nervous system. It was first isolated from liver concentrate by Rickes and his coworkers in 1948 and structural elucidated by Hodgkin and her coworkers in the late 1950's. It is currently commercially available as a tablet and as an injectable.

Therapeutically, vitamin B_{12} is employed in the treatment of a variety of B_{12} deficiency afflictions, principally anemias such as pernicious and diplyllobothrium latum. Although the minimum daily requirement of vitamin B_{12} is approximately 0.1 μg, the generally prescribed initial therapeutic dose is 100 to 1000 μg given intramuscularly. Maintenance therapy with vitamin B_{12} is usually 100 μg intramuscularly, monthly and must be continued for life.

Since pernicious anemia is often a disease of later years when many sufferers have reduced muscle mass or are atrophic, repeated intramuscular injections of vitamin B_{12} can be inconvenient, painful and often require doctor's visits. In some cases at least in the early stages, hospitalization is required. As a result, there is a need for a more convenient, less painful and less expensive method of administering vitamin B_{12}, particularly one that would not require hospitalization or repeated physician contacts.

Unfortunately, up to the present time no efficient method of administering B_{12} which will achieve therapeutically useful blood levels of the vitamin except parenteral administration has been devised.

In 1953 and 1954 Monto et al in Am. J. Med. Sci., 223, 113 (1953) and Arch. of Int. Med. 93,219 (1954) described administration of B_{12} by nasal inhalation and instillation. The vehicles for administration were aqueous isotonic sodium chloride solution and lactose powder. Although the results were reported as effective, safe and economical, the fact is that parenteral administration remains the only method regarded by the medical community as a safe, reliable and effective method for treating vitamin B_{12} deficiencies in humans. No composition for nasal inhalation or instillation has become commercially available for nasal administration to mammals. Neither have there been any further publications describing nasal inhalation or instillation of which applicant is aware.

The difficulty with nasal instillation by nasal dosage as the procedure is described in the cited articles is that most of the B_{12} passes immediately into the throat. It is not in contact with the nasal mucosa for a sufficient period of time to permit useful and uniform absorption. Most of the B_{12} so administered is, in fact wasted.

Compositions have now been discovered for the nasal administration of B_{12} which can be kept in contact with the nasal mucosa for an extended period of time. During the time the compositions are in such contact, the B_{12} is uniformly absorbed from the compositions through the nasal mucosa and is then uniformly distributed systemically. The use of the compositions, because of the efficiency with which the B_{12} is absorbed allows the use much lesser amounts of B_{12} than is normally present in parenteral B_{12} compositions. Moreover, since the patient can self administer the B_{12}, the need for hospitalization or physician contacts is minimized and may even be eliminated.

THE INVENTION

This invention provides vitamin B_{12} containing compositions specifically formulated for nasal administration which will, unlike aqueous isotonic sodium chloride compositions, remain in contact with the nasal mucosa for a sufficiently long period of time to permit consistent, continuous and uniform absorption of therapeutically effective amounts of a vitamin B_{12} through the nasal mucous membrane.

The invention, therefore comprises compositions containing a therapeutically effective amount of a vitamin B_{12}, such compositions being sufficiently viscous to maintain themselves in the nasal passages for a period of time which is long enough so that most of the B_{12} is absorbed. The compositions are stable, easy to handle, and may be self administered by the patient.

More specifically the compositions of the invention are for nasal administration and contain a therapeutically effective amount of a vitamin B_{12} in an isotonic aqueous buffer at a pH of from about 4 to 6. The compositions may be in the form of gels, lotions, ointments, creams and the like and will contain a sufficient amount of a thickening agent so that the viscosity is from about 2500 to 6500 cps, although more viscous compositions even up to 10,000 cps may be employed. The preferred compositions have a viscosity of 2500 to 5000 cps, since above that range they become more difficult to administer.

Due to the efficiency with which the B_{12} is adsorbed from the compositions of this invention, a therapeutically effective amount of B_{12} for nasal administration will normally be appreciably less than for other methods of administration. Typically the concentration of B_{12} in a composition of the invention will be 0.05% to 1% by weight based on the total weight. In dosage unit forms the dosage will normally be from about 50 to 1000 micrograms.

The pH of the compositions of this invention is from about 4 to 6. At this pH, B_{12} is stable so that the compositions have a shelf life which may be a year or more. Additionally, at this pH, irritation of the nasal mucosa is minimal. The pH is maintained with a physiologically acceptable buffer composition suitably an acetate, citrate, phosphate, phthalate, borate, or other buffer.

Acetate and citrate buffers are preferred for convenience and economy.

The isotonicity of the composition is accomplished using sodium chloride, or other pharmaceutically acceptable agent such as dextrose, boric acid, sodium tartrate or other inorganic or organic solute. Sodium chloride is preferred particularly for buffers containing sodium ions.

Viscosity of the compositions is maintained at the selected level using a therapeutically acceptable thick-

ening agent. Methyl cellulose is preferred because it is easily and economically available and is easy to work with. Other suitable thickening agents include, for example, xanthan gum, carboxymethyl cellulose, hydroxypropyl cellulose, carbomer, and the like. The preferred concentration of the thickener will depend upon the agent selected. The important point is to use an amount which will achieve the selected viscosity.

Preferred compositions within the scope of this invention will contain a humectant to inhibit drying of the mucous membrane and to prevent irritation. Any of a variety of humectants can be employed including, for example sorbitol, propylene glycol or glycerol. As with the thickeners, the concentration will vary with the selected agent, although the presence or absence of these agents, or their concentration is not an essential feature of the invention.

An enhanced absorption of B_{12} across the mucous membrane can be accomplished employing a surfactant. Typically useful surfactants for these therapeutic compositions include polyoxyethylene derivatives of fatty acid partial esters of sorbitol anhydrides such as Tween 80, Polyoxyl 40 Stearate, Polyoxyethylene 50 Stearate and Octoxynol. The usual concentration is from 1% to 10% based on the total weight.

A preservative is generally employed to increase the shelf life of the compositions. Benzyl alcohol is suitable, although a variety of preservatives including, for example, Parabens, thimerosal, chlorobutanol, or benzalkonium chloride may also be employed. A suitable concentration of the preservative will be from 0.02% to 2% based on the total weight, although there may be appreciable variation depending upon the agent selected.

The therapeutically effective compositions of this invention are prepared by mixing the ingredients following generally accepted procedures. For example, the selected components may be simply mixed in a blender, or other standard machine to produce a concentrated mixture which is then adjusted to the final concentration and viscosity by the addition of water.

A typical composition of this invention contains the following components per 100 ml.

Benzyl alcohol, NF: 1.50 ml
Sodium chloride, NSP: 0.82 gm
Methyl cellulose, USP (400 cps): 2.00 gm
Acetic acid, NF: 0.10 gm
Sodium acetate (anhyd, USP): 0.27 gm
Sorbitol soln., USP: 5.00 ml
Cyanocobalamine, USP: 0.10 gm
Water, purified: q.s. 100.00 ml

The viscosity of the formulation is about 4500 cps. The pH is about 5.

The following non-limiting examples are given by way of illustration only and are not to be considered limitations of this invention of which many apparent variations are possible without departing from the spirit or scope thereof.

EXAMPLE 1

The following compositions prepared by mixing.

A

Phenylmercuric Acetate NF: 0.002 g
Boric Acid NF: 1.740 g
Methylcellulose (4000 CPS) USP: 2.000 g
Acetic Acid NF: 0.100 g
Sodium Acetate (Anhydrous) USP: 0.270 g
Glycerin USP: 5.000 ml
Cyanocobalamin USP: 0.100 g
Water, Purified USP: q.s. 100.000 ml

B

Benzalkonium Chloride NF: 0.020 g
Potassium Chloride USP: 1.080 g
Hydroxyethyl Cellulose (3500–4000 CPS) NF: 1.000 g
Acetic Acid NF: 0.100 g
Sodium Acetate (Anhydrous) USQ: 0.270 g
Propylene Glocol USP: 5.000 ml
Cyanocobalamin USP: 1.000 g
Water, Purified USP: q.s. 100.000 ml

C

Thimerosal USP: 0.002 g
Dextrose USP: 5.120 g
Polysorbate 80 USP: 10.000 g
Methylcellulose (4000 CPS) USP: 1.33 g
Acetic Acid NF: 0.100 g
Sodium Acetate (Anhydrous) USP: 0.270 g
Glycerin USP: 5.000 ml
Cyanocobalamin USP: 0.500 ml
Water, Purified: q.s. 100.000 ml

D

Methylparaben NF: 0.020 g
Propylparaben NF: 0.010 g
Sodium Chloride USP: 0.820 g
Xanthan Gum NF: 2.000 g
Acetic Acid NF: 0.100 g
Sodium Acetate (Anhydrous) USP: 0.270 g
Propylene Glycol USP: 5.000 g
Cyanocobalamin USP: 0.200 g
Water, Purified: q.s. 100.000 ml

The viscosities of the compositions are within the range defined above.

The typical composition disclosed above just prior to the examples was tested in humans in order to determine quantitative increases in B_{12} Blood Levels following nasal administration. Three normal volunteers received 0.1 cc of the cited composition (100 μg B_{12}) inserted nasally with a nasal syringe applicator. Serial Blood Samples were drawn from the subjects at 0, 0.05, 0.08, 0.16, 0.25, 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, and 24 hours following dosing and assayed for B_{12} content by radioimmunoassay.

It was found that in less than 15 minutes after administration the serum level of B_{12} was significantly elevated and that significantly elevated blood levels were maintained during the full 24 hours of the study period.

The actual plasma blood levels of B_{12}, in the subjects following its nasal administration in the above cited composition, were:

TIME (hours)	PLASMA LEVELS (Picograms)
0	599
0.05	631
0.08	628
0.16	674
0.25	754
0.5	729
1.0	804
2.0	794
3.0	769
4.0	727
6.0	752
8.0	803
24.0	729

An additional and similar study was performed with three human subjects using the same composition in which 0.2 cc was administered intranasally (200 μg B12). The actual plasma blood levels obtained were:

TIME (hours)	PLASMA LEVELS (Picograms)
0.0	591
0.05	630
0.08	637
0.16	680
0.25	699
0.5	742
1.0	809
2.0	849
3.0	786
4.0	764
6.0	722
8.0	742
24.0	675

EXAMPLE 2

A composition of this invention containing the following components per 100 ml was prepared.

Benzyl Alcohol NF: 1.50 ml
Sodium Chloride USP: 0.82 g
Methyl Cellulose (400 cps.): 133. g
Acetic Acid NF: 0.10 g
Sodium Acetate (Anhydrous): 0.27 g
Sorbitol Solution USP: 5.00 ml
Cyanocoabalamin USP: 0.10 g
Water, Purified USP: q.s. 100.000 ml

This composition was tested in three humans as described in the previous example. The nasal administration of 200 μg of B_{12} in 0.2 cc gave the following serum B_{12} levels:

TIME (hours)	PLASMA LEVELS (Picograms)
0.0	731
0.05	734
0.08	725
0.16	845
0.25	837
0.5	940
1.0	975
2.0	1027
3.0	1038
4.0	1002
6.0	969
8.0	945
24.0	925

Again it was found that in approximately 15 minutes after administration the serum level of B_{12} was significantly elevated and that significantly elevated blood levels were maintained during the full 24 hours of the study period.

EXAMPLE 3

The following comparative experiment was conducted on forty normal, human, adult volunteers to compare the availability, speed of availability, and duration of availability of B_{12} administered by various routes. Commercially available oral and sublingual tablets were compared with the compositions of this invention which were administered orally. All samples were tested by high performance liquid chromatography for B_{12} per dosage unit was as follows:

Methyl Cellulose: 20 gm
Sodium Citrate: 3.2 gm
Citric Acid: 1.2 gm
Benzalkonium chloride 50%: 0.4 ml
Cyanocolalamine: 2.5 gm
Purified Water q.s. to: 100 ml

The composition used to prepare the 400 mcg intranasal dosage unit was identical except that it contained 4.0 gm. of cyanocolalamine.

Serial blood samples were from the subjects at 0, 5, 1, 2, 4, 8, 24, 48 and 72 hours following dosing and assayed for B_{12} content by radioimmunoassay.

The results are shown in FIGS. 1, 2, 3 and 4 in which concentration in picograms per ml. is plotted against time. The results are also summarized in table 1. In the table, the baseline is the B_{12} average concentration of B_{12} in the volunteer group prior to B_{12} administration.

From an analysis of the figures and the tables, the following unexpected advantages for nasal administration of B_{12} in the compositions of this invention will be apparent:

1. Increased blood levels at lower dosages.
2. Maximum blood levels achieved more rapidly, and at lower dosage levels.
3. High blood levels maintained for entire period of test as indicated by larger areas under the carve.
4. Substantially higher blood levels at lower dosages even two days after administration.

TABLE 1

A COMPARISON OF THE BIOAVAILABILITY OF VITAMIN B_{12} FOLLOWING INTRANASAL, ORAL, AND SUBLINGUAL ADMINISTRATION IN NORMAL SUBJECTS

Number of Subjects	Vitamin B_{12} Treatment	Average Baseline pc/ml	Average Maximum Increase in Plasma B_{12} Concentration	Average time to Reach Maximum B_{12} Plasma Concentration	Average Area Under The Curve (pcg hr/ml)	Average Increase In Plasma B_{12} Concentration in 48 hrs. (pcg/ml)
10	500 mcg Oral Tablet	665.8	233.51 pcg/ml	25.60 Hours	9.503	92.6
10	500 mcg Sublingual Tablet	599.8	196.64 pcg/ml	5.70 Hours	6.010	51.1
10	250 mcg Intranasal	577.2	1167.31 pcg/ml	2.5 Hours	24.266	193.5
10	400 mcg	472.1	1967.98 pcg/ml	1.61 Hours*	28.690	178.9

*A 24:00 hour data point was considered and outlier and eliminated from the calculation of the average.

What is claimed is:

1. A therapeutic composition for nasal administration comprising a therapeutically effective amount of a vitamin B_{12}, a pharmaceutically acceptable isotonic aqueous buffer to provide a pH of from about 4 to 6 and sufficient pharmaceutically acceptable thickening agent so that the viscosity of the composition is from about 2500 to 10,000 cps.

2. A therapeutic composition of claim 1 wherein the vitamin B_{12} is cyanocobalamin.

3. A composition as in claim 1 or 2 additionally containing from about 1% to 10% by weight of a humectant.

4. A composition as in claim 1 or 2 additionally containing from about 0.2% to 2% by weight of a surfactant.

5. A composition as in claim 1 or 2 additionally containing from about 1% to 10% by weight of a humectant and from about 0.2% to 2% by weight of a surfactant.

6. A therapeutic composition as in claim 1 wherein the thickening agent is methyl cellulose.

7. A therapeutic composition of claim 6 wherein the vitamin B_{12} is cyanocobalamin.

8. A therapeutic composition of claim 6 or 7 additionally containing from about 1% to 10% by weight of a humectant and from about 0.2% to 2% by weight of a surfactant.

9. A therapeutic composition for nasal administration in dosage unit form comprising from 50 to 1000 micrograms of a vitamin B_{12}, a pharmaceutically acceptable isotonic aqueous buffer to provide a pH of from about 4 to 6 and sufficient pharmaceutically acceptable thickening agent so that the viscosity of the composition is from about 2500 to 10,000 cps.

10. A therapeutic composition as in claim 9 wherein the vitamin B_{12} is cyanocobalamin.

11. A therapeutic composition as in claim 9 or 10 additionally containing from about 1% to 10% by weight of a humectant.

12. A therapeutic composition as in claim 9 or 10 additionally containing from about 0.2% to 2% by weight of a surfactant.

13. A therapeutic composition as in claim 9 or 10 additionally containing from about 1% to 10% by weight of a surfactant.

14. A therapeutic composition as in claim 9 wherein the thickening agent is methyl cellulose.

15. A therapeutic composition as in claim 14 wherein the vitamin B_{12} is a cyanocobalamin.

16. A therapeutic composition as in claim 14 or 15 additionally containing from about 1% to 10% by weight of a humectant and from about 0.2% to 2% by weight of a surfactant.

17. A method of treating a human for vitamin B_{12} deficiency which comprises nasal administering to a human in need of such treatment a composition comprising a therapeutically effective amount of a vitamin B_{12}, a pharmaceutically acceptable isotonic aqueous buffer to provide a pH of from about 4 to 6 and sufficient pharmaceutically acceptable thickening agent so that the viscosity of the composition is from about 2500 to 10,000 cps.

18. A method as in claim 17 wherein the vitamin B_{12} is cyanocobalamin.

19. A method as in claim 17 or 18 wherein the composition additionally contains from about 1% to 10% by weight of a humectant.

20. A method as in claim 17 or 18 wherein the composition additionally contains from about 0.2% to 2% by weight of a surfactant.

21. A method as in claim 17 or 18 wherein the composition additionally contains from about 1% to 10% by weight of a humectant and from about 0.2% to 2% by weight of a surfactant.

22. A method as in claim 17 wherein the thickening agent is methyl cellulose.

23. A method as in claim 22 wherein the vitamin B_{12} is cyanocobalamin.

24. A method as in claim 22 or 23 wherein the composition additionally contains from about 1% to 10% by weight of a humectant and from about 0.2% to 2% by weight of a surfactant.

25. A composition as in claim 1 wherein the viscosity is from 2500 to 6500 cps.

26. A composition as in claim 9 wherein the viscosity is from 2500 to 6500 cps.

27. A method as in claim 17 wherein the viscosity of the composition is from 2500 to 6500 cps.

* * * * *

EXHIBIT C

BRIEF DESCRIPTION OF ACTIVITIES UNDERTAKEN BY APPLICANT DURING THE REGULATORY REVIEW PERIOD FOR NASCOBAL

January 21, 1985	Application for Investigational New Drug (IND) filed with the FDA
February 7, 1985	Telephone conversation With Dr. M. K. Bennett of the FDA about the Chemistry, Manufacturing & Compliance (CMC) information
February 24, 1985	Initiated Phase I Study (Protocol 160-01)
May 21, 1985	Reported Phase I results, submitted the validation of analytical method and animal toxicological data to the FDA. Also, submitted protocol for another Phase I Study (Protocol 160-02) to the FDA
June 17, 1985	Received a letter from the FDA allowing to proceed with additional Phase I studies
July 8, 1985	Letter to Dr. S. Sobel of the FDA in response to the FDA letter of June 17, 1985
August 27, 1985	Letter to Dr. S. Sobel of the FDA about labeling on clinical supplies and CMC issues
September 11, 1985	Letter to Ms. K. Ellsworth of the FDA about scheduling of a meeting to discuss Phase I results
October 16, 1985	Letter to Dr. S. Sobel of the FDA about pre-conference memo for the conference scheduled for October 31, 1985
November 5, 1985	Letter to Dr. S. Sobel of the FDA providing minutes of the October 31, 1985 meeting
November 19, 1985	Letter to Dr. S. Sobel of the FDA about Phase I results recalculated following the October 31, 1985 meeting
January 8, 1986	Letter to Dr. S. Sobel of the FDA about the compassionate use of the product discussed at the October 31, 1985 meeting
February 3, 1986	Letter to Dr. S. Sobel of the FDA about Phase III Protocols and about clinical investigators

February 12, 1986	Initiated technical work on the nasal mucosal irritation study
March 27, 1986	Completed the nasal mucosal irritation study
April 16, 1986	Received study report of 15 Day Nasal Mucosal Irritation Study from Findley Research
May 1, 1986	Finalized Phase III Protocols
May 14, 1986	Letter to Dr. S. Sobel of the FDA regarding the results of the nasal toxicological study, the additional clinical site and the investigators
May 19, 1986	Letter to Ms. K. Ellsworth of the FDA about a request for a meeting with the FDA
June 17, 1986	Obtained IRB approval for Phase III Study
August 15, 1986	Obtained Statement of Investigator from Dr. R. Bender of Southern California Permanente Medical Group concerning Phase III Study
August 28, 1986	Letter from Dr. D. Pet of Nutmeg IRB of NMRC (concerning Phase III Study
September 15, 1986	Supplied clinical supplies to southern california Permanente Medical Group for Phase III Study
October 10, 1986	Completed the development of HPLC method for cyanocobalamin nasal gel
October 30, 1986	Letter to Dr. S. Sobel of the FDA about modified Phase III Protocols and about the various clinical sites
November 12, 1986	Meeting between Dr. M. Bennett of the FDA and Mr. I. Nudelman of Nastech, at the FDA concerning the CMC Section of the NDA
November 14, 1986	Received specifications of 1 mL nasal applicator as part of container closure system
November 21, 1986	Letter from Mr. R. T. LeNoir of safety and Regulatory Affairs Specialist concerning grant of permission to refer to confidential information supplied to the FDA by Himont, Inc.

December 19, 1986	Letter from Dr. S. Sobel of the FDA concerning patient informed consent
December 29, 1986	Letter to Southern California Permanente Medical Group concerning patient informed consent form revisions
January 12, 1987	Letter and submission to Dr. S. Sobel of the FDA on the CMC information
February 6, 1987	Obtained IRB approval for protocol modifications for Phase III Study at Southern California Permanente Medical Group
February 26, 1987	Letter to Dr. S. Sobel of the FDA concerning revisions of the patient informed consent form for Phase III Study
March 9, 1987	Provided clinical supplies to Veterans Medical Center for Phase III Study
March 12, 1987	Sent copy of the modified Phase III Protocol to Veterans Medical Center
April 30, 1987	Obtained IRB approval from Mount Sinai Medical Center for Phase III Study
May 21, 1987	Submitted CMC Section for NDA to the FDA
May 29, 1987	Letter from Mr. R. Eastep of the FDA concerning the receipt of the CMC Section
June 2, 1987	Submitted additional Phase III Protocol D
June 19, 1987	Letter from Dr. S. Sobel of the FDA concerning approving Phase III Protocol
July 16, 1987	Provided additional clinical supplies to Veterans Medical Center for Phase III Study
August 21, 1987	Provided additional clinical supplies to Veterans Medical Center for Phase III Study
September 11, 1987	Submitted the remainder (clinical section) of NDA No. 19-722 to complete NDA for submission purposes

September 30, 1987	Telephone conversation between Dr. M. Bennett of the FDA and Mr. I. Nudelman of Nastech concerning the CMC Section of the NDA No. 19-722
October 23, 1987	Submitted additional CMC information to the FDA
November 10, 1987	Letter from the FDA informing the unacceptability of the NDA No. 19-722 for filing
November 18, 1987	Telephone conversation with the FDA concerning the letter of November 10, 1987
November 24, 1987	Letter to Dr. S. Sobel of the FDA requesting for a meeting regarding the NDA No. 19-722
December 15, 1987	Provided clinical supplies to Veterans Medical Center for Phase III Study
January 5, 1988	Letter to Dr. S. Sobel of the FDA confirming a meeting between the FDA and Nastech on January 21, 1988
January 21, 1988	Letter to Dr. S. Sobel of the FDA concerning diagnosis of pernicious anemia in two patients
January 21, 1987	Met with the FDA concerning the NDA No. 19-722
February 10, 1988	Letter to Dr. S. Sobel of the FDA containing minutes of the January 21, 1988 meeting
March 10, 1988	Updated the revised specifications of vitamin B12
April 15, 1988	Letter to Mr. T. Hope of the FDA enclosing samples of cyanocobalamin nasal gel for analysis and Amendment 1 to the NDA
May 2, 1988	Submitted additional samples of cyanocobalamin nasal gel to the FDA
June 30, 1988	Letter to Dr. S. Sobel of the FDA enclosing Amendment 2 to the NDA No. 19-722
July 28, 1988	Provided clinical supplies to Veterans Medical Center for Phase III Study

August 30, 1988	Letter from the FDA informing that resubmitted NDA No. 19-722 of June 30, 1988 is not acceptable for filing
September 27, 1988	Letter to Dr. S. Sobel of the FDA requesting for a meeting concerning the rejection letter of August 30, 1988
October 27, 1988	Provided clinical supplies to Veterans Medical Center for Phase III Study
November 18, 1988	Letter to Ms. K. Ellsworth of the FDA confirming a meeting with the FDA on December 1, 1988
December 1, 1988	Met with the FDA about the NDA rejection letter of August 30, 1988
December 8, 1988	Submitted Amendment 3 to the NDA No. 19-722 containing additional clinical results, to Dr. S. Sobel of the FDA
December 14, 1988	Letter from Ms. K. Worth of the FDA to Nastech acknowledging the receipt of Amendment 3 to the NDA No. 19-722
January 9, 1989	Letter to Dr. J. Hunt of the FDA concerning meeting of January 18, 1989 to discuss issues raised at the December 1, 1988 Meeting
January 17, 1989	Telephone conference with Dr. J. Hunt to discuss the upcoming meeting of January 18, 1989
January 18, 1989	Cancellation of the meeting with the FDA scheduled for January 18, 1989 since Dr. Hunt of FDA informed that adequate clinical study results in support of the acceptance for filing NDA No. 19-722 had been previously submitted
January 24, 1989	Telephone conference with Dr. J. Hunt of the FDA concerning clinical trials contained in the NDA No. 19-722
February 14, 1989	Letter from Ms. K. Ellsworth of the FDA confirming the filing date of February 12, 1989 for the NDA No. 19-722
February 17, 1989	Submitted additional copy of Amendment 3 to the NDA No. 19-722, to Dr. J. Hunt of the FDA pursuant to his request made on February 17, 1989

June 12, 1989	Received a telephone call from Dr. A. Gordon and Dr. J. Hunt of the FDA requesting clarification of some pharmacokinetics information submitted in Amendment 3 to the NDA No. 19-722
June 13, 1989	Letter from Dr. N. Colman, Nastech's principal investigator, to Dr.. J. Wenig of Nastech concerning vitamin B12 assay method
June 29, 1989	Submitted Amendment 4 to the NDA No. 19-722, to Dr. S. Sobel of the FDA. This amendment contains clarification of some pharmacokinetics information contained in Amendment 3, as requested by Dr. J. Hunt on June 12, 1989
July 6, 1989	Letter from Dr. S. Sobel of the FDA acknowledging the receipt of Amendment 4 to the NDA No. 19-722. He also informed Nastech that Amendment 4 was a major amendment and therefore will take 60 days to review it
July 6, 1989	Telephone conference with Dr. M. Bennett of the FDA concerning packaging and labeling DMFs
July 7, 1989	Submitted Amendment 5 to the NDA No. 19-722, in response to Dr. M. Bennett's request of July 6, 1989
July 14, 1989	Received a request from Dr. S. Sobel of the FDA to submit an annual report on additional studies conducted toward NDA No. 19-722
July 28, 1989	Letter from Dr. S. Sobel of the FDA informing Nastech of the deficiencies in the NDA No. 19-722
August 16, 1989	Submitted Amendment 6 to the NDA No. 19-722, in response to Dr. S. Sobel's letter of July 28, 1989
September 15, 1989	Telephone conference with Dr. E. Herman of the FDA concerning clinical studies contained in Amendment 2 to the NDA No. 19-722. Additional information was requested by Dr. Herman
September 21 1989	Submitted Annual Report on additional studies conducted toward NDA No. 19-722 at the request of Dr. Sobel made on July 14, 1989
October 5, 1989	Submitted of Addendum to Amendment 2 to the NDA No. 19-722, to Dr. E. Herman and Dr. S. Sobel both of the FDA. This addendum contained the information requested by Dr. Herman on September 15, 1989

October 23, 1989	Telephone conference with Dr. M. Bennett of the FDA requesting additional stability results of vitamin B12 nasal gel
October 25, 1989	Submitted stability information requested by Dr. M. Bennett of the FDA on October 23, 1989
November 1989	Nastech decided to stop using contract manufacturer for producing vitamin B12 gel and began to establish manufacturing process in-house
December 1989	Began manufacturing, filling, labelling and packaging of vitamin B12 nasal gel in-house
October 30, 1989	Dr. M. Bennett of the FDA informed Nastech of deficiencies in the CMC Section of NDA No. 19-722
January 12, 1990	Letter to Dr. S. Sobel of the FDA requesting a meeting to discuss the status of review of clinical information contained in NDA No. 19-722
January 24, 1990	Telephone conference with Dr. G. Trendel and others of the FDA concerning the meeting request made on January 12, 1990. A lengthy discussion on the clinical portion of NDA No. 19-722 took place
January 30, 1990	Letter from Dr S. Sobel of the FDA informing Nastech of a 30 day extension in the review process
February 13, 1990	Letter to Dr. S. Sobel expressing Nastech's concerns on the length of the review time of clinical information in NDA No. 19-722 and also acknowledging receipt of the FDA letter of January 30, 1990
February 26, 1990	Submitted Amendment 7 to the NDA No. 19-722, to Dr. S. Sobel of the FDA. This amendment contained a new CMC Section
February 26, 1990	Submitted Amendment 8 to the NDA 19-722, to Dr. S. Sobel of the FDA. This amendment contained an updated clinical information
March 29, 1990	Submitted Addendum to Amendment 7 to NDA No. 19-722, to Dr. S. Sobel of the FDA. This addendum contained results of on-going stability tests, as mentioned in Amendment 7
March 30, 190	Received a telephone call from Dr. R. Young of the FDA informing Nastech that NDA No. 19-722 was randomly selected for a clinical audit

April 4, 1990	Submitted a list of all clinical sites, investigators and protocols to the FDA in response to FDA's Dr. Young's phone call of March 30, 1990
April 5, 1990	Dr. R. Young of the FDA requested for additional information on the clinical studies contained in NDA No. 19-722. This information was in relation to the clinical audit
April 16, 1990	Submitted information to the FDA requested by Dr. R. Young of the FDA on April 5, 1990
April 26, 1990	Met with the FDA concerning clinical issues of Amendment 8 to NDA No. 19-722
April 23-27, 30, 1990	Pre-approval inspection by the FDA
April 26, 1990	Memo from Dr. S. Sobel of the FDA concerning the assay validation data of cyanocobalamin, dosing patients, and package insert. The memo was given to Nastech at the April 26, 1990 meeting at the FDA
May 8, 1990	Received a "483" from the FDA in response to the pre-approval inspection
June 5, 1990	Submitted Amendment 9 to NDA No. 19-722, to Dr. S. Sobel of the FDA, in response to the meeting with the FDA held on April 26, 1990
June 18, 1990	Letter to Dr. S. Sobel of the FDA in response to additional biopharmaceutical issues raised in the memo given by the FDA to Nastech at the conclusion of April 26, 1990 meeting
June 28, 1990	Submitted information to the FDA on the safety aspects of vitamin B12 nasal gel
July 19, 1990	Telephone conference with Dr. M. Bennett of the FDA concerning updated stability data of vitamin B12 nasal gel
July 24, 1990	Submitted Addendum 2 to Amendment 7 to NDA No. 19-722 in response to FDA's Dr. M. Bennett's telephone request of July 19, 1990
October 17, 1990	Submitted responses to the 483 items received on May 8, 1990 from the FDA as a result of pre-approval inspection

November 16, 1990	Letter from Dr. S. Sobel of the FDA informing Nastech that Vitamin B12 nasal gel was not recommended for approval
November 26, 1990	Letter to Dr. S. Sobel of the FDA informing him of Nastech's intention to file an Amendment to NDA No. 19-722 in response to FDA's non-approvable letter of November 16, 1990. It also requested for a meeting.
December 1990	Gathered information for response to the FDA's non-approvable letter of November 16, 1990
January 11, 1991	Letter to Dr. S. Sobel of the FDA concerning the agenda of the upcoming meeting with the FDA on January 15, 1991
January 15, 1991	Met with the FDA to discuss deficiencies in NDA No. 19-722 mentioned in FDA's non-approvable letter of November 16, 1990
January 31, 1991	Letter to Dr. J. Hunt of the FDA providing information on one patient requested at the January 15, 1991 meeting with the FDA
February 1, 1991	Letter from Dr. D. Gordon of the FDA acknowledging receipt of Nastech's January 31, 1991 letter and requesting that clinical data be presented in another format
February 19, 1991	Submitted a draft protocol to Dr. D. Gordon of the FDA
March 11, 1991	Submitted Amendment 10 to NDA No. 19-722. It contained the new format of data presentation as requested by Dr. J. Hunt of the FDA
May 9, 1991	Letter from Dr. S. Sobel of the FDA acknowledging receipt of the protocol and asking for revision of the protocol submitted by Nastech on February 19, 1991
May 14, 1991	Called Ms. S. Olmsteadt of the FDA inquiring whether or not the FDA received Amendment 10 to NDA No. 19-722 submitted by Nastech on March 11, 1991
May 22, 1991	Submitted revision in the protocol as requested by Dr. S. Sobel in his letter of May 9, 1991
July 5, 1991	Letter from Dr. S. Sobel of the FDA providing his comments on the revision of the protocol submitted by Nastech on May 22, 1991

August 5, 1991	Preparation of the Informed Consent Form for the Proposed Phase III Study
August 29, 1991	Revisions in the Informed Consent Form
September 10, 1991	Preparation of Form 1572 for the Proposed Phase III Study
October 9, 1991	Recruitment of patients for the Proposed Phase III Study
October 11, 1991	Signed a contract with NMRC Site for the Proposed Phase III Study
October 29, 1991	Preparation of Randomization Scheme for the Proposed Phase III Study
November 5, 1991	Supplied NMRC Site with clinical preparations for use in Phase III Study
November 18, 1991	Letter to NMRC Site regarding Form 1572 and protocol changes
December 20, 1991	Letter to Dr. S. Sobel of the FDA informing him of the status of the on-going Phase III Study
January 17, 1992	Nastech visited NMRC Site to monitor the on-going Phase III Study
January 23, 1991	Supplied NMRC Site with clinical preparations for use in Phase III Study
January 31, 1992	Nastech visited NMRC Site to monitor the on-going Phase III Study
February 7, 1991	Letter from Dr. S. Sobel of the FDA agreeing with Nastech's letter of December 20, 1991
March 20, 1992	Received status report from NMRC Site for the on-going Phase III Study
April 14, 1992	Letter to Dr. S. Sobel of the FDA providing additional information on the on-going Phase III Study
April 14, 1992	Supplied NMRC Site with clinical preparations for use in Phase III Study
May 20, 1992	Nastech visited NMRC Site to monitor the on-going Phase III Study

May 29, 1992	Letter to Dr. S. Sobel of the FDA providing him with a revised Informed Consent Form
June 5, 1992	Nastech recruited additional patients for the on-going Phase III Study
July 31, 1992	Letter to Dr. S. Sobel of the FDA informing him of the additional clinical sites chosen
August 11, 1992	Received status report from NMRC Site for the on-going Phase III Study
September 11, 1992	Received status report from NMRC Site for the on-going Phase II Study
September 25, 1992	Received status report from NMRC Site for the on-going Phase III Study
October 15, 1992	Received status report from NMRC Site for the on-going Phase III Study
October 21, 1992	Received status report from NMRC Site for the on-going Phase III Study
November 30, 1992	Supplied NMRC with clinical preparations for the on-going Phase III Study
December 16, 1992	Nastech visited NMRC Site to monitor on-going Phase III Study
January 20, 1993	Met with NMRC personnel at the site to discuss Phase III Study results
February 8, 1993	Submitted pre-amendment report (for Amendment 11 in preparation) to Dr. S. Sobel of the FDA
February 24, 1993	Submitted Addendum 3 to Amendment 7 to NDA No. 19-722, to Dr. D. Wu of the FDA, which contained new CMC information
March 8, 1993	Letter to NMRC Site concerning changes in Case Report Forms
April 14, 1993	Letter to Mr. R. Hedin of the FDA regarding the submission made by Nastech on February 8, 1993

April 16, 1993	Telephone call from Mr. R. Hedin of the FDA regarding Nastech's letter of April 14, 1993 regarding the length of review of information submitted by Nastech on February 8, 1993
April 23, 1993	Letter from NMRC Site concerning changes in Case Report Forms
April 29, 1993	Called Mr. R. Hedin of the FDA and requested to facilitate the review process of the information submitted by Nastech on February 8, 1993
April 29, 1993	Called Dr. D. Gordon and E. Herman both of the FDA and discussed the information submitted by Nastech on February 8, 1993
May 10, 1993	Submitted a copy of the February 8, 1993 submission to Dr. D. Gordon of the FDA
May 11, 1993	Called Dr. D. Gordon of the FDA to confirm the receipt of information submitted by Nastech to him on May 10, 1993
May 19, 1993	Called Dr. D. Gordon of the FDA regarding Nastech's May 10, 1993 submission to him
May 20, 1993	Letter from Dr. G. Trendel of the FDA informing Nastech that 26 patient study was adequate
May 27, 1993	Letter from Dr. F. O. Kelsey of the FDA to Dr. N. Colman regarding FDA's site visit
June 1, 1993	Letter to Dr. G. Trendel of the FDA thanking her for her letter of May 20, 1993
June 3, 1993	Nastech visited NMRC Site to discuss clinical data
July 7, 1993	Letter from Dr. S. Sobel of the FDA informing that Nastech could re-submit the NDA with clinical data from 26 patients as opposed to 30 patients originally agreed upon
July 27, 193	Received final report from NMRC Site for the Phase III Study
August 24, 1993	Submitted Amendment 11 to NDA No. 19-722 to Dr. S. Sobel of the FDA. This amendment contained clinical information
September 23, 1993	Submitted supplemental information (to Amendment 11) to Dr. G. Gordon in response to his request

November 3, 1993	Telephone conversation with Dr. D. . Gordon of the FDA regarding labelling of vitamin B12 nasal gel product
November 3, 1993	Submitted labelling information to Dr. D. Gordon of the FDA
November 12, 1993	Submitted additional pharmacokinetics information to Dr. D. Gordon of the FDA in support of Amendment 11 to NDA No. 19-722
November 22, 1993	Call from Dr. D. Wu of the FDA regarding the CMC Section of NDA No. 19-722
November 24, 1993	Submitted revised CMC information to Dr. D. Wu in response to his call of November 22, 1993
December 7, 1993	Call from Dr. D. Wu of the FDA regarding the container closure system
January 3, 1994	Call from Dr. D. Gordon of the FDA regarding container closure system
January 21, 1994	Call from Dr. D. Wu of the FDA regarding container closure system and requested additional stability data
January 25, 1994	Called Dr. D. Wu of the FDA to discuss labelling issues
January 26, 1994	Submitted additional stability information to Dr. D. Wu of the FDA
Jan. 6-27, 1994	Pre-approval inspection by the FDA
January 27, 1994	Received "483" from the FDA
February 1, 1994	Call from Dr. D. Wu of the FDA regarding container closure system
February 7, 1994	Submitted response to "483" to Mr. E. T. Warner of the FDA
February 9, 1994	Call from Dr. Thomas of the FDA regarding container closure system
February 9, 1994	Submitted results of nasal applicator tube evaluation to Dr. D. Wu of the FDA
February 14, 1994	Call from Dr. D. Wu regarding data submitted by Nastech on February 9, 1994

February 15, 1994	Call from Dr. M. Thomas of the FDA regarding data submitted by Nastech on February 9, 1994, and also requesting re-plot certain data from Amendment 11 to NDA No. 19-722
February 22, 1994	Called Dr. M. Thomas of the FDA informing him that Nastech would send him the information requested by him on February 15, 1994. Also, he requested for another study evaluating nasal applicator tube
February 22, 1994	Submitted re-plotted graphs from Amendment 11 to Dr. M. Thomas of the FDA, and informed him of Nastech's plans to conduct another study to evaluate the nasal applicator tube in volunteers
February 23, 1994	Received fax message from Dr. M. Thomas requesting additional re-ploting of data from Amendment 11 to NDA No. 19-722
February 23, 1994	Call from Dr. M. Thomas of the FDA asking Nastech to submit a protocol of the applicator evaluation study prior to conducting it.
February 23, 1994	Submitted re-plotted data to Dr. M. Thomas of the FDA
February 23, 1994	Call from Dr. M. Thomas of the FDA asking that error bars be added to the graphs submitted by Nastech on February 23, 1994
February 24, 1994	Submitted the applicator evaluation protocol and new graphs with error bars added to them
March 1, 1994	Call from Dr. M. Thomas of the FDA asking for revisions in the applicator evaluation protocol submitted by Nastech on February 24, 1994
March 4, 1994	Called Dr. M. Thomas of the FDA and discussed revisions in the applicator evaluation protocol suggested by him on March 1, 1994.
March 8, 1994	Called Dr. M. Thomas of the FDA inquiring about FDA's response to revisions in the applicator evaluation protocol
March 9, 1994	Called Dr. M. Thomas of the FDA informing him that Nastech would start the applicator evaluation study in volunteers on March 11, 1994.
March 10, 1994	Submitted final protocol for the applicator evaluation to Dr. M. Thomas of the FDA

April 8, 1994	Submitted Amendment 12 to NDA No. 19-722, to Dr. S. Sobel of the FDA, containing results of the applicator tube evaluation in volunteers
April 21, 1994	Call from Mr. R. Hedin of the FDA requesting for two additional copies of Amendment 12 to NDA No. 19-722
April 21, 1994	Submitted two additional copies of Amendment 12 to Mr. R. Hedin of the FDA in response to his request of April 21, 1994
April 25, 1994	Call from Dr. M. Thomas and discussed Amendment 12 to NDA No. 19-722 and clinical data from Amendment 11
April 27, 1994	Submitted to Dr. M. Thomas of the FDA information previously submitted to the FDA on February 9, 22, 23, 24, 1994 and on March 10, 1994
April 27, 1994	Submitted additional information to Dr. M. Thomas in response to his call of April 25, 1994
May 18, 1994	Submitted updated stability data to Dr. D. Wu of the FDA
May 23, 1994	Called Dr. M. Thomas of the FDA inquiring status of review of NDA No. 19-722
June 13, 1994	Called Mr. R. Hedin of the FDA regarding the review status of NDA No. 19-722 and was informed that the review was in final stages of completion
July 5, 1994	Called Dr. M. Thomas and Mr. R. Hedin both of the FDA regarding the status of review of NDA No. 19-722
July 11, 1994	Called Dr. M. Thomas of the FDA regarding the review status of NDA No. 19-722
July 19, 1994	Called Mr. R. Hedin of the FDA regarding the review status of NDA No. 19-722
July 21, 1994	Received a letter of non-approval (i.e., rejection) of NDA No. 19-722 from Dr. S. Sobel of the FDA
July 26, 1994	Called Dr. M. Thomas and Mr. R. Hedin regarding the non-approval letter of July 21, 1994

July 27, 1994	Called Mr. J. Hunt of the FDA regarding the non-approval letter of July 21, 1994
July 28, 1994	Letter to Dr. S. Sobel of the FDA acknowledging the receipt of non-approval letter of July 21, 1994 and confirming Nastech's plans to re-file the NDA
July 29, 1994	Called Dr. S. Sobel of the FDA requesting a meeting
August 1, 1994	Letter from Dr. S. Sobel of the FDA confirming Nastech's telephone call of July 29, 1994
August 2, 1994	Call from Mr. R. Hedin of the FDA to schedule a meeting on September 12, 1994
August 8, 1994	Called Mr. R. Hedin of the FDA requesting that Dr. D. Wu of the FDA also be present at the meeting on September 12, 1994
August 8, 1994	Submitted an agenda for the September 12, 1994 meeting at the FDA, to Mr. R. Hedin
August 8, 1994	Call from Dr. G. Trendel of the FDA confirming September 12, 1994 meeting at the FDA
August 9, 1994	Call from Mr. R. Hedin of the FDA indicating that Dr. D. Wu of the FDA would be present at the meeting on September 12, 1994
September 12, 1994	Met with the FDA regarding re-filing of NDA No. 19-722
September 12, 1994	Submitted updated stability data to Dr. D. Wu of the FDA
September 13, 1994	Letter to Dr. M. Thomas regarding issues raised at the September 12, 1994 meeting at the FDA
September 14, 1994	Submitted a draft protocol of the proposed clinical study to Dr. M. Thomas of the FDA
September 16, 1994	Submitted a draft protocol of the proposed clinical study to Dr. G. Trendel and Mr. J. Hunt both of the FDA
September 23, 1994	Called Dr. G. Trendel of the FDA inquiring the status of review of the clinical study protocol

October 3, 1994	Received minutes of September 12, 1994 meeting held at the FDA, from Dr. C. Spires
October 3, 1994	Call from Dr. C. Spires of the FDA indicating that Nastech's cGMP status was unacceptable as per the FDA inspection of January 1994
October 4, 1994	Called Dr. C. Spires of the FDA regarding her call of October 3, 1994
October 4, 1994	Called Ms. L. Avieta of the FDA regarding cGMP compliance status of Nastech
October 7, 1994	Called Dr. D. Wu of the FDA regarding stability protocol for a new container closure system
October 11, 1994	Called Mr. J. Sollazo of the FDA regarding cGMP compliance status of Nastech
October 12, 1994	Called Dr. C. Spires of the FDA regarding cGMP compliance status of Nastech
October 12, 1994	Called Dr. M. Thomas of the FDA regarding review of clinical protocol submitted on September 14, 1994
October 20, 1994	Letter to Dr. C. Spires of the FDA requesting her to expedite the cGMP compliance issue
October 21, 1994	Call from Dr. C. Spires of the FDA suggesting that Nastech call Mr. D. Dolesky of the FDA regarding the cGMP compliance issue
October 21, 1994	Called Mr. D. Dolesky of the FDA regarding the cGMP compliance issue, and was informed that Nastech call Mr. T. Platz of the FDA about this issue
October 21, 1994	Called Dr. M. Thomas of the FDA regarding review of clinical protocol submitted on September 14, 1994
October 25, 1994	Called Mr. T. Platz of the FDA and learned why Nastech was deemed not to be in cGMP compliance
October 25, 1994	Submitted a copy of response to "483" to Mr. T. Platz of the FDA in response to a telephone conversation with him on October 25, 1994

October 28, 1994	Letter to Dr. M. Thomas of the FDA inquiring the status of review of clinical protocol submitted on September 14, 1994
November 1, 1994	Called Dr. M. Thomas of the FDA regarding clinical protocol and learned that the review would be completed by November 7, 1994
November 2, 1994	Called Dr. C. Spires of the FDA and expressed Nastech's concerns on the time it had taken on part of the FDA to review the clinical protocol submitted on September 14, 1994
November 8, 1994	Received minutes of September 12, 1994 meeting held at the FDA, from Dr. C. Spires of the FDA
November 9, 1994	Call from Dr. C. Spires of the FDA providing changes in the clinical protocol submitted on September 14, 1994
December 1, 1994	Submitted corrective actions taken on "483" items, to Mr. T. Platz of the FDA
December 13, 1994	Submitted a preliminary validation package of metered dose nasal gel actuator, to Dr. M. Thomas, Dr. G. Trendel, Dr. D. Wu, Dr. S. Sobel and Mr. J. Hunt, all of the FDA
December 20, 1994	Call from Dr. C. Spires of the FDA confirming the receipt of submission of December 13, 1994
January 6, 1995	Letter from E. T. Warner of the FDA confirming that the corrective actions taken by Nastech and communicated to the FDA on December 1, 1994, were adequate
January 17, 1995	Submitted support information on the upcoming clinical studies to Dr. S. Sobel of the FDA
January 20, 1995	Nastech signed a contract with NMRC to conduct the proposed clinical study in PA patients
February 21, 1995	Letter to Dr. W. Wecksler of SKB regarding the analytical method to assay vitamin B12 in human blood
March 8, 1995	File memo from Dr. W. E. Gannon of Nastech on the status of on-going clinical study

April 5, 1995	Letter to Dr. S. Sobel of the FDA providing support information on the on-going clinical study
April 13, 1995	Received status report from NMRC Site for the on-going clinical study
April 20, 1995	Received IRB approval for the GFI Clinical Site
April 20, 1995	Report on the visit of NMRC by Dr. W. E. Gannon
May 10, 1995	Letter to Dr. B. Levy of NMRC regarding additional clinical sites
May 30, 1995	Letter to Dr. S. Sobel of the FDA providing support documentation on the on-going clinical studies
June 1, 1995	Letter from Ms. D. J. Racine of GFI Site supplying additional IRB information
June 6, 1995	Received status report on clinical studies from NMRC Site
June 6, 1995	Received report on the visit of NMRC Site by Dr. W. E. Gannon
June 28, 1995	Forwarded an update on clinical supplies inventory to NMRC
July 15, 1995	Received patient status report from GFI Site
July 21, 1995	Received report on the visit of GFI Site by Dr. W. E. Gannon
August 9, 1995	Received status report on dosing of patients from GFI Site
August 23, 1995	Received a fax message from Ms. M. C. English of SKB regarding vitamin B12 assay in human blood
September 7, 1995	Received report on close-out visit of GFI Site by dr. W. E. Gannon
September 14, 1995	Letter from J. H. Keach of NMRC Site regarding case report form corrections
October 13, 1995	Letter from Ms. D. J. Racine of GFI Site regarding the final report of the clinical study
October 16, 1995	Fax message to Mr. J. Keach of NMRC Site regarding patient case report forms

November 21, 1995	File memo on the re-assays of serum samples done at SKB, by Mr. J. C. deMereles and Dr. W. E. Gannon
November 29, 1995	Letter from Ms. M. C. English of SKB regarding vitamin B12 assays in human serum
December 15, 1995	File memo from Mr. J. C. deMeireles on the validation report of vitamin B12 assay in human serum
December 21, 1995	Fax message from M. C. Whelden of NMRC Site regarding patient blood draws
January 1996	Planned and manufactured three validation batches of vitamin B12 nasal gel
February 1995	Sent the bulk gel batches to C P Packaging Co. in NJ for filling, labelling and packaging
February 1996	Placed the three validation batches in final package form on full and formal stability
March 19, 1996	Finalized the validation report of metered dose nasal gel actuator
April 10, 1996	Called Ms. J. Weber of the FDA inquiring whom should Nastech submit the clinical amendment
April 11, 1996	Submitted Amendment 13 to NDA No. 19-722, to Dr. S. Sobel of the FDA. It contained clinical information
May 8, 1996	Submitted Amendment 14 to NDA No. 19-722, to Dr. S. Sobel of the FDA. It contained CMC information
June 6, 1996	Call from Dr. D. Wu asking for additional information on the container closure system
June 7, 1996	Called Dr. D. Wu and provided information requested by him on June 6, 1996
June 24, 1996	Call from Dr. M. Fossler of the FDA regarding data in Amendment 13 to NDA No. 19-722

June 24, 1996	Submitted Addendum to Amendment 14 to NDA No. 19-722, to Dr. D. Wu of the FDA. It contained additional stability data
June 24, 1996	Call from Dr. D. Wu of the FDA regarding Amendment 14 to NDA No. 19-722
June 26, 1996	Submitted computer disk containing some data from Amendment 13 to NDA No. 19-722, to Dr. M. Fossler of the FDA
June 27, 1996	Submitted clarification of some CMC information to the FDA
July 24, 1996	Call from Dr. T. Sze regarding site inspection of Roussel, the manufacturer of vitamin B12
August 9, 1996	Call from Dr. M. Fossler of the FDA regarding clinical data
August, 1996	FDA made site visits of C P Packaging Co., Loricon Labs, and other contract labs/cos.
Sept 5,6,11,16,17, '96	Pre-approval inspection by the FDA
October, 1996	FDA made a site visit of clinical site and SKB Labs
October 3, 1996	Received "483" from the FDA
October 7, 1996	Call from Dr. D. Wu of the FDA regarding container closure system
October 10, 1996	Call from Mr. S. McCort of the FDA regarding the package insert
October 11, 1996	Submitted package insert information on a computer disk to the FDA
October 16, 1996	Responded to "483"
October 17, 1996	Submitted information on closure container system to Dr. D. Wu
October 29, 1996	Letter from Mr. F. Mattiasich of the FDA acknowledging 483 response
October 31, 1996	Teleconference with FDA personnel about analytical method issues
November 1, 1996	Received package insert changes from Mr. S. McCort of the FDA
November 5, 1996	Resolved all CMC issues with Dr. D. Wu of he FDA

NOVEMBER 5, 1996 RECEIVED APPROVAL TO MARKET NASCOBAL (CYANOCOBALAMIN NASAL GEL) FROM THE FDA

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of: Jeffrey Wenig

Patent No.: 4,724,231

Serial No.: 06/848,690

For: NASAL COMPOSITIONS CONTAINING VITAMIN B_{12}

Docket: 719-69

Issued: February 9, 1988

Filed: April 8, 1986

Box Patent Ext.
Assistant Commissioner for Patents
Washington, D.C. 20231

POWER OF ATTORNEY BY ASSIGNEE OF ENTIRE INTEREST

Sir:

Nastech Pharmaceutical Company Inc., of 45 Davids Drive, Hauppauge, New York 11788, as assignee of record of U.S. Patent No.: 4,724,231, hereby appoints the following attorneys:

Charles R. Hoffmann, Reg. No. 24,102; Ronald J. Baron, Reg. No. 29,281; Gerald T. Bodner, Reg. No. 30,449; Alan M. Sack, Reg. No. 31,874; A. Thomas Kammer, Reg. No. 28,226; Arlene D. Morris, Reg. No. 32,657; R. Glenn Schroeder, Reg. No. 34,720; Glenn T. Henneberger, Reg. No. 36,074; Livia Boyadjian, Reg. No. 34,781; Sean W. O'Dea, Reg. No. 37,690; Lindsay S. Adams, Reg. No. 36,425; Paul J. Otterstedt, Reg. No. 37,411; Irving N. Feit, Reg. No. 28,601; William E. Lewis, Reg. No. 39,274; and Paul D. Ackerman, Reg. No. 39,891, each of them of HOFFMANN & BARON, 350 Jericho Turnpike, Jericho, New York 11753; and Daniel A. Scola, Jr., Reg. No. 29,855; Salvatore J. Abbruzzese, Reg. No. 30,152; Kirk M. Miles, Reg. No. 37,891; Kevin C. Hooper, Reg. No. P-40,402; and Robert F. Chisolm, Reg. No. 39,939, each of them of HOFFMANN & BARON, 1055 Parsippany Boulevard, Parsippany, New Jersey 07054,

to apply for an extension of the term of said patent, to make alterations and amendments therein, and transact all business in the U.S. Patent and Trademark Office connected therewith, and request that all further correspondence be conducted with Hoffmann & Baron as indicated below.

SEND CORRESPONDENCE TO:

Gerald T. Bodner, Esq.
Hoffmann & Baron
350 Jericho Turnpike
Jericho, New York 11753

DIRECT TELEPHONE CALLS TO:

Lindsay S. Adams, Esq.

Nastech PharmaceuticalCompany, Inc.
(type or print identity of assignee of entire interest)

45 Davids Drive
Address

Hauppauge, New York 11788

[X] Recorded in PTO on April 8, 1986
Reel 4567
Frame 732

[ ] Recorded herewith

ASSIGNEE CERTIFICATION UNDER 37 CFR 3.73(b)

I, the undersigned, have reviewed all the documents in the chain of title of the patent matter identified above and, to the best of my knowledge and belief, title is in the assignee identified above.

I, hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements, and the like so made, are punishable by fine or imprisonment, or both, under Section 1001, Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the patent.

(Signature)

Date 1/3/97

Vincent D. Romeo R. Ph., Ph.D.
(type or print name of person authorized to sign on behalf of assignee)

President and CEO
Title

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of: Jeffrey Wenig

Patent No.: 4,724,231

Serial No.: 06/848,690

For: NASAL COMPOSITIONS CONTAINING VITAMIN B_{12}

Docket: 719-69

Issued: February 9, 1988

Filed: April 8, 1986

Date: January 3, 1997

EXPRESS MAIL CERTIFICATE
Date 1-3-97 Label No. EM290462959US
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Kim Beaulieu Kim Beaulieu
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Assistant Commissioner for Patents
Washington, D.C. 20231

CERTIFICATION OF DUPLICATE COPY

Sir:

I, the undersigned, hereby certify that attached herewith is a true and accurate copy of the application for term extension under 35 U.S.C. §156 for U.S. Patent No.: 4,724,231 being filed herewith.

Respectfully submitted,

Lindsay S. Adams
Attorney for Applicant
Registration No.: 36,425

Hoffmann & Baron
350 Jericho Turnpike
Jericho, New York 11753
(516) 822-3550
LSA/kb

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of: Jeffrey Wenig

Patent No.: 4,724,231

Serial No.: 06/848,690

For: NASAL COMPOSITIONS CONTAINING VITAMIN B_{12}

Docket: 719-69

Issued: February 9, 1988

Filed: April 8, 1986

Date: January 3, 1997

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Assistant Commissioner for Patents
Washington, D.C. 20231

LETTER OF TRANSMITTAL OF APPLICATTON FOR EXTENSION OF PATENT TERM

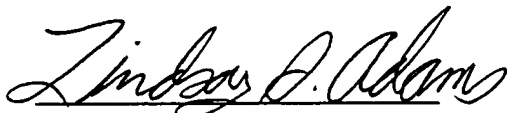
Sir:

Transmitted herewith is an application for extension of the patent term under 35 U.S.C. §156 for U.S. Patent No.: 4,724,231. The application includes Exhibits A-C, a Declaration pursuant to 37 C.F.R. §1.740(b), a Power of Attorney executed by the Applicant, and a duplicate of the application papers, certified as such.

The filing fee of $1090.00 in accordance with 37 C.F.R. § 1.20(j) is also enclosed herewith. The Commissioner is hereby authorized to charge any additional fees, or credit

any overpayment, to Deposit Account No.: 08-2461. Two additional copies of this sheet are enclosed.

Respectfully submitted,



Lindsay S. Adams
Attorney for Applicant
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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of: Jeffrey Wenig

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Assistant Commissioner for Patents
Washington, D.C. 20231

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Kim Beaulieu Kim Beaulieu
Name (Print) Signature

DECLARATION PURSUANT TO 37 C.F.R. §1.740(b) FOR APPLICATION FOR PATENT EXTENSION UNDER 35 U.S.C. §156

Sir:

The undersigned, an Attorney registered to practice before the U.S. Patent and Trademark Office and having the general authority from the owners of U.S. Patent No. 4,724,231 to act on behalf of the owners of said patent (i.e., the Applicant), as indicated in the Power of Attorney being submitted herewith, hereby states:

1. I have reviewed and understand the contents of the application for patent extension of U.S. Patent No. 4,724,231 being submitted herewith pursuant to 35 U.S.C. §156;

2. I believe U.S. Patent No. 4,724,231 is subject to an extension pursuant to 37 C.F.R. §1.710 and believe that the term of extension claimed in the

application filed contemporaneously herewith is justified under 35 U.S.C. §156 and under the applicable regulations; and

3. I believe that U.S. Patent No. 4,724,231 for which an extension is being sought meets all the conditions for an extension of the term of said patent, as set forth in 37 C.F.R. §1.720.

I further state that the above statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that any willful false statements may jeopardize the validity of this patent.

Date: 1/3/97

Respectfully submitted,

Lindsay S. Adams
Registration No.: 36,425
Attorney for Applicant

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